# Guidance for Industry

## Medical Imaging Drug and Biological Products

## Part 1: Conducting Safety Assessments

### *Draft Guidance*

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**May 2003**
**Clinical Medical**

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## Part 1: Conducting Safety Assessments

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# Guidance for Industry[1]
# Medical Imaging Drug and Biological Products
# Part 1: Conducting Safety Assessments

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. INTRODUCTION

This guidance is one of three guidances intended to assist developers of medical imaging drug and biological products (*medical imaging agents*) in planning and coordinating their clinical investigations and preparing and submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), abbreviated NDAs (ANDAs), and supplements to NDAs or BLAs. The three guidances are*: Part 1: Conducting Safety Assessments of Medical Imaging Agents*; *Part 2: Clinical Indications*; and *Part 3: Design, Analysis, and Interpretation of Clinical Studies.*

Medical imaging agents generally are governed by the same regulations as other drug and biological products.[2] However, because medical imaging agents are used to diagnose and monitor diseases or conditions, development programs for medical imaging agents can be tailored to reflect how these products are used. Specifically, this guidance discusses our recommendations on how to conduct safety assessments of medical imaging agents.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

[1] This guidance has been prepared by the Division of Medical Imaging and Radiopharmaceutical Drug Products in the Center for Drug Evaluation and Research (CDER) and the Office of Therapeutics Research and Review in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Sponsors developing medical imaging agents should be familiar with Agency regulations and guidances pertaining to the development of these products.

be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## II. SCOPE — TYPES OF MEDICAL IMAGING AGENTS

This guidance discusses medical imaging agents that are administered in vivo and are used for diagnosis or monitoring. Included are medical imaging agents used with medical imaging techniques such as radiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and radionuclide imaging. The guidance is not intended to cover agents for in vitro diagnostic uses, or agents used for treatment or prevention of a disease or condition.[3]

Medical imaging agents can be classified into at least two general categories:

### A. Contrast Agents

Contrast agents improve the visualization of tissues, organs, and physiologic processes by increasing the relative difference of imaging signal intensities in adjacent regions of the body. Products include (1) iodinated compounds used in radiography and CT; (2) paramagnetic metallic ions (such as ions of gadolinium, iron, and manganese) linked to a variety of molecules and used in MRI; and (3) microbubbles, microaerosomes, and related microparticles used in diagnostic ultrasonography.

### B. Diagnostic Radiopharmaceuticals

As used in this guidance, a *diagnostic radiopharmaceutical* is (1) an article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons or (2) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such an article.[4] As stated in the preamble to FDA's proposed rule on Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring, the Agency interprets this definition to include articles that exhibit spontaneous disintegration leading to the reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons (63 FR 28301 at 28303; May 22, 1998).

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[3] The guidance is not intended to apply to the development of research drugs that do not have clinical usefulness. The Agency recognizes the potential of imaging as a research tool, and some of the principles of the guidance may be applicable. Sponsors of such products are urged to contact the appropriate review division for advice on product development.

[4] 21 CFR 315.2 and 601.31.

Diagnostic radiopharmaceuticals are generally radioactive drug or biological products that contain a radionuclide that may be linked to a ligand or carrier.[5] These products are used in planar imaging, single photon emission computed tomography (SPECT), positron emission tomography (PET), or with other radiation detection probes.

Diagnostic radiopharmaceuticals used for imaging typically have two distinct components.

- A radionuclide that can be detected in vivo (e.g., technetium-99m, iodine-123, indium-111).

  The radionuclide typically is a radioactive molecule with a relatively short physical half-life that emits radioactive decay photons having sufficient energy to penetrate the tissue mass of the patient. These photons can then be detected with imaging devices or other detectors

- A nonradioactive component that delivers the molecule to specific areas within the body.

  This nonradionuclidic portion of the diagnostic radiopharmaceutical often is an organic molecule such as a carbohydrate, lipid, nucleic acid, peptide, small protein, or antibody. In general, the purpose of the nonradioactive component is to direct the radionuclide to a specific body location or process.

As technology advances, new products may emerge that do not fit into these traditional categories (e.g., agents for optical imaging, magnetic resonance spectroscopy, combined contrast and functional imaging). It is anticipated, however, that the general principles discussed here could apply to these new diagnostic products. Developers of these products should contact the appropriate reviewing division for advice on product development.

## III. GENERAL CONSIDERATIONS FOR SAFETY ASSESSMENTS OF MEDICAL IMAGING AGENTS

### A. Medical Imaging Agent Characteristics Relevant to Safety

The following sections discuss the special characteristics of a medical imaging agent that can lead to a more focused safety evaluation. These characteristics include its dose or mass, route of administration, frequency of use, and biological, physical, and effective half-lives.[6]

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[5] In this guidance, the terms *ligand* and *carrier* refer to the entire nonradionuclidic portion of the diagnostic radiopharmaceutical.

[6] See also 21 CFR 315.6 on evaluation of safety. When a medical imaging agent does not possess any special characteristics, complete standard safety assessments should be performed.

#### *1. Dose or Mass*

Some medical imaging agents can be administered at low mass doses. For example, the mass of a single dose of a diagnostic radiopharmaceutical often can be relatively small because device technologies can typically detect small amounts of a radionuclide. When a medical imaging agent is administered at a mass dose that is at the low end of the dose-response curve for adverse events, dose-related adverse events are less likely to occur.

#### *2. Route of Administration*

Some medical imaging agents are administered by routes that decrease the likelihood of systemic adverse events. For example, medical imaging agents that are administered as contrast media for radiographic examination of the gastrointestinal tract (e.g., barium sulfate) can be administered orally, through an oral tube, or rectally. In patients with normal gastrointestinal tracts, many of these products are not absorbed. Accordingly, systemic adverse events are less likely to occur in these patients. Therefore, if a sponsor demonstrates that such a product is not absorbed systemically in the population proposed for use, the product may be able to undergo a more efficient safety evaluation that primarily assesses local organ system toxicity, toxicities that are predictable (e.g., volume effects, aspiration), and effects after intraperitoneal exposure (e.g., after gastrointestinal perforation). However, if the product will be used in patients with gastrointestinal pathologies that increase absorption, we recommend that additional nonclinical and clinical safety evaluations be performed.

#### *3. Frequency of Use*

Many medical imaging agents, including both contrast agents and diagnostic radiopharmaceuticals, are administered relatively infrequently or as single doses. Accordingly, adverse events that are related to long-term use or to accumulation are less likely to occur with these agents than with agents that are administered chronically. Therefore, the nonclinical and clinical development programs for such products can omit long-term, repeat-dose safety studies. That is, long-term repeat-dose toxicology studies (i.e., 3 months duration or longer) are normally not necessary for single-use agents. However, in clinical settings where it is possible that the medical imaging agent will be administered repeatedly (e.g., to monitor disease progression), we recommend that repeat-dose studies be performed to assess safety and efficacy.

Biological medical imaging agents are frequently immunogenic, and the development of antibodies after intermittent, repeated administration can alter the pharmacokinetics, biodistribution, safety, and/or imaging properties of such agents and, potentially, of immunologically related agents. Studies of immunogenicity in animal models are generally of limited value. Therefore, we recommend that clinical data assessing the repeat use of a biological imaging agent be obtained prior to application for licensure of such an agent.

#### *4. Biological, Physical, and Effective Half-Lives*

Diagnostic radiopharmaceuticals often use radionuclides with short physical half-lives or that are excreted rapidly. The biological, physical, and effective half-lives of diagnostic radiopharmaceuticals are incorporated into radiation dosimetry evaluations[7] that require an understanding of the kinetics of the distribution and excretion of the radionuclide and its mode of decay. We recommend that biological, physical, and effective half-lives be considered in planning appropriate safety and dosimetry evaluations of diagnostic radiopharmaceuticals.

## B. Performance of Nonclinical Safety Assessments

We recommend that the nonclinical development strategy for an agent be based on sound scientific principles; the agent's unique chemistry (including, for example, those of its components, metabolites, and impurities); and the agent's intended use. Sponsors are encouraged to consult with the Agency before submitting an IND application and during product development. In part, the number and types of nonclinical studies we would recommend would depend on the phase of the development, what is known about the agent or its pharmacologic class, its proposed use, and the indicated patient population.

In the discussion that follows, a distinction is made between drug products and biological products. Existing specific guidance for biological products is referenced but not repeated here (see section III.B.2.).

### *1. Nonclinical Safety Assessments for Nonbiological Drug Products*

#### a. Timing of Nonclinical Studies Submitted to an IND Application

We recommend appropriate timing of nonclinical studies to facilitate the timely conduct of clinical trials (including appropriate safety monitoring based on findings in nonclinical studies) and to reduce the unnecessary use of animals and other resources.[8] The recommended timing of nonclinical studies for medical imaging drugs is summarized in Table 1.

#### b. Contrast Agents

Because of the characteristics of contrast drug products (e.g., variable biologic half-life) and the way they are used, we recommend that nonclinical safety evaluations of such drug products be made more efficient with the following modifications:

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[7] *Biological half-life* is the time needed for a human or animal to remove, by biological elimination, half of the amount of a substance that has been administered. *Effective half-life* is the time needed for a radionuclide in a human or animal to decrease its activity by half as a combined result of biological elimination and radioactive decay. *Physical half-life* is the time needed for half of the population of atoms of a particular radioactive substance to disintegrate to another nuclear form.

[8] See the guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*.

- Long-term (i.e., greater than 3 months), repeat-dose toxicity studies in animals usually can be omitted. (Exceptions are products with long residence time, e.g., > 90 days.)

- Long-term rodent carcinogenicity studies usually can be omitted.[9] We recommend that a justified waiver request be submitted.[10]

- Reproductive toxicology studies often can be limited to an evaluation of embryonic and fetal toxicities in rats and rabbits and to evaluations of reproductive organs in other short-term toxicity studies.[11] However, we recommend a justification be provided for any studies of reproductive toxicology that are not performed, and we recommend a formal request be made to waive them.

We recommend that studies be conducted to address the large mass dose and volume (especially for iodinated contrast materials that are administered intravenously); osmolality effects; potential transmetalation of complexes of gadolinium, manganese, or iron (generally MRI drugs); potential effects of tissue or cellular accumulation on organ function (particularly if the drug is intended to image a diseased human organ system); and the chemical, physiological, and physical effects of ultrasound microbubble drugs (e.g., coalescence, aggregation, margination, and cavitation).

[9] Circumstances in which carcinogenicity testing may be recommended are summarized in the guidance *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

[10] Requests for waivers of reproductive toxicity studies can be made under §§ 312.10 for INDs and 314.90 for NDAs.

[11] See the guidance *S5A Detection of Toxicity to Reproduction for Medicinal Products* and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.

**Table 1: Timing of Nonclinical Studies for Nonbiological Products Submitted to an IND**

| Study Type | Before Phase 1 | Before Phase 2 | Before Phase 3 | Before NDA |
|---|---|---|---|---|
| Safety pharmacology | Major organs,[a] and human organ systems the drug is intended to visualize | | | |
| Toxicokinetic pharmacokinetic | See ICH guidances | | | |
| Expanded single-dose toxicity | Expanded acute single dose [b] | Perform if short-term repeat-dose toxicity and nonexpanded single-dose are submitted prior to phase 1[c] | | |
| Short-term multiple dose toxicity | | Repeat-dose toxicity | | |
| Local tolerance studies | Based on route-irritancy, blood compatibility, protein flocculation, misadministration, extravasation | | | |
| Radiation dosimetry | If applicable | | | |
| Genotoxicity | In vitro [d] | Complete standard battery | | |
| Immunotoxicity | | If molecular structure, class concern, clinical or nonclinical signal | | |
| Reproductive and developmental toxicity | | | Needed or waiver obtained [d] | |
| Drug interaction | | | | As needed |
| Other based on data results | | | | As needed |

(a) See the guidance *S7A Safety Pharmacology Studies for Human Pharmaceutical*.
(b) See the guidance *Single Dose Acute Testing for Pharmaceuticals*.
(c) When repeat-dose toxicity studies have been performed, but single-dose toxicology studies have not, dose selection for initial human studies will likely be based on the results of the no-adverse-effect level (NOAEL) obtained in the repeat-dose study. The likely result will be a dose selection for initial human administration that is lower than if the dose selection had been based on the results of acute, single-dose toxicity studies.
(d) See radiopharmaceutical discussion in section III.B.1.c of this document.

c. Diagnostic Radiopharmaceuticals (Nonbiological Products)

Because of the characteristics of diagnostic radiopharmaceuticals and the way they are used, we recommend that nonclinical safety evaluations of these drugs be made more efficient by the following modifications:

- Long-term, repeat-dose toxicity studies in animals typically can be omitted.

- Long-term rodent carcinogenicity studies usually can be omitted.

- Reproductive toxicology studies can be waived when adequate scientific justification is provided.[12]

- The radioactive component of the agent represents a likely genotoxic hazard**.** We recommend that components other than the radionuclide be considered separately because they may be genotoxins or teratogens, causing effects that exceed those of the radioactivity alone. Genotoxicity studies may be waived if adequate scientific justification is provided.[13]

  We recommend that special safety considerations for diagnostic radiopharmaceuticals include verification of the mass dose of the radiolabeled and unlabeled moiety; assessment of the mass, toxic potency, and receptor interactions for any unlabeled moiety; assessment of potential pharmacologic or physiologic effects due to molecules that bind with receptors or enzymes; and evaluation of all components in the final formulation for toxicity (e.g., excipients, reducing drugs, stabilizers, anti-oxidants, chelators, impurities, and residual solvents). We recommend that the special safety considerations include an analysis of particle size (for products containing particles) and an assessment of instability manifested by aggregation or precipitation. We also recommend that an individual component be tested if specific toxicological concerns are identified or if toxicological data for that component are lacking.

*2. Nonclinical Safety Assessments for Biological Products*

Many biological products raise relatively distinct nonclinical issues (e.g., immunogenicity and species specificity). We recommend the following Agency documents be reviewed for guidance on the preclinical evaluation of biological medical imaging agents:

- *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

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[12] See footnote 11.

[13] See guidances *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals*.

- *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*.

Sponsors are encouraged to consult with the appropriate reviewing division for additional information when needed.

# IV. CLINICAL SAFETY ASSESSMENTS

Benefits of the use of the medical imaging agent must outweigh the risks to the patient. Risks include both those related to administration of the agent and the risks of incorrect diagnostic information. Incorrect diagnostic information includes inaccurate structural, functional, physiological, or biochemical information; false positive or false negative diagnostic determinations; and information leading to inappropriate decisions in diagnostic or therapeutic management. FDA weighs benefits and risks when making its decision about whether to approve a marketing application (e.g., NDA or BLA).

## A. Group 1 and 2 Medical Imaging Agents

The special characteristics of medical imaging agents may allow for a more efficient clinical safety program. This guidance defines two general categories for medical imaging agents: Group 1 and Group 2. The extent of clinical safety monitoring and evaluation that we recommend differs for these two categories. Medical imaging agents considered by FDA as Group 1 medical imaging agents are usually better suited than Group 2 imaging agents for a more focused clinical safety evaluation during development. We recommend that those agents considered by the Agency as Group 2 medical imaging agents undergo standard clinical safety evaluations in clinical trials throughout development.

FDA anticipates that it should be able to grant most Group 1 designations based on the safety-margin criteria at the end of phase 1, after animal studies and initial human trials have been completed.

### *1. Group 1 Medical Imaging Agents*

For purposes of this guidance, a Group 1 medical imaging agent generally exhibits the following three characteristics:

- The medical imaging agent meets *either* the safety-margin considerations or the clinical-use considerations described below (see Sections B.1 and B.2, respectively).
- The medical imaging agent is not a biological product,[14, 15] and

[14] Medical imaging products that are biological products, such as radiolabeled cells, monoclonal antibodies, or monoclonal antibody fragments, would not normally be considered Group 1 medical imaging agents because of their potential to elicit immunologic responses.

- The medical imaging agent does not predominantly emit alpha or beta particles.[16]

Note that under the safety margin criteria (see Section IV.B), medical imaging agents that are administered in low mass doses to humans (e.g., diagnostic radiopharmaceuticals) usually are more likely to be considered Group 1 than those administered in higher mass doses. There are important exceptions, including cases where the medical imaging agents are likely to be immunogenic (e.g., biological products) when the pharmacologic response exists at a low mass dose, or when the medical imaging agents cause adverse reactions that are not dose-related (e.g., idiosyncratic drug reactions).

We recommend that standard clinical safety evaluations be performed in all clinical investigations of medical imaging agents until FDA notifies you that it considers your drug to be in Group 1. Once this occurs, reduced human safety monitoring in subsequent human trials may be appropriate.

- For example, human safety monitoring may be limited to recording adverse events and monitoring particular organs or tissues of interest for toxicity (such as organs that showed toxicity in the animal studies or the tissues in which the medical imaging agent localizes).

A product's status as a Group 1 agent designation can be retained throughout its development if safety concerns are not raised subsequently in nonclinical and clinical studies. If safety concerns are identified, FDA may consider the medical imaging agent as Group 2 for the remainder of product development.

### *2. Group 2 Medical Imaging Agents*

For purposes of this Guidance, Group 2 medical imaging agents are generally medical imaging drug or biological products that do not fall under the considerations for Group 1 medical imaging agents. All biological products belong to Group 2. Group 2 medical imaging agents are biologically active in animal studies or in human studies when administered at dosages that are similar to those intended for clinical use.[17]

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[15] See also the final regulation, Adverse Experience Reporting Requirements for Licensed Biological Products (59 FR 54042; October 27, 1994).

[16] Group 1 diagnostic radiopharmaceuticals may include radionuclides, ligands, and carriers that are known to be biologically inactive. This group may include radionuclides, ligands, and carriers used at radiation doses or mass dosages that are similar to, or less than, those used previously. This group also may include radionuclides, ligands, and carriers that have been documented not to produce adverse reactions.

[17] Group 2 diagnostic radiopharmaceuticals can also include radionuclides and carriers that are known to be biologically active. This group includes radionuclides and carriers used at radiation doses or mass dosages that are higher than those used previously, including radionuclides and carriers that have been documented to poduce adverse reactions.

For Group 2 medical imaging agents, *standard clinical safety evaluations* include serial assessments of patient symptoms, physical signs, clinical laboratory tests (e.g., blood chemistry, hematology, coagulation profiles, urinalyses), other tests (e.g., electrocardiograms as appropriate), and adverse events. We recommend that additional specialized evaluations be performed when appropriate (e.g., immunological evaluations, creatine kinase isoenzymes), or if a particular toxicity is deemed possible based on animal studies or the known chemical or pharmacological properties of the medical imaging agent. We recommend that the duration of clinical monitoring be sufficient to identify possible effects that may lag behind those predicted by pharmacokinetic analyses. If some of these standard clinical safety evaluations are felt to be unnecessary, this should be discussed with the reviewing division. We recommend that sponsors seek FDA comment on the clinical safety monitoring plans in clinical studies before such studies are initiated.

## B. Considerations For Whether a Radiopharmaceutical is Group 1 or 2

### *1. Safety-Margin Criteria*

Under the safety-margin considerations, medical imaging agents may be considered Group 1 if the results of nonclinical studies ***and*** initial human experience are consistent with the conditions outlined below:

#### a. Results of nonclinical studies

To be considered for a Group 1 designation under the safety-margin criteria, we recommend that a medical imaging agent have an adequately documented margin of safety as assessed in the nonclinical studies outlined in the following list:[18]

- We recommend that the no-observed-adverse-effect level (NOAEL)[19] in expanded-acute, single-dose toxicity studies in suitable animal species be at least one hundred times (100x) greater than the maximal dose and dosage to be used in human studies. We further recommend that such expanded, acute, single-dose toxicity studies be completed before the medical imaging agent is introduced into humans (see Section III.B.1).

  Also, whether a medical imaging agent can be considered Group 1 may be influenced by a NOAEL (100-fold of the maximum human dose based on body surface area) derived from a nonexpanded acute toxicity study.

[18] In addition, the medical imaging agent should meet the conditions described for the results of initial human experience (see Section IV.B.1.b).

[19] For purposes of Groups 1 and 2 in this section of this guidance, the term *no-observed-adverse-effect-level (NOAEL)* is defined as the highest dose tested in animals with no adverse effects. (See guidance *A Harmonized Approach to Estimating the Safe Starting Dose for Clinical Trials of Therapeutics in Healthy Volunteers.*)

- We recommend that the NOAEL in safety pharmacology studies in suitable animal species be at least one hundred times (100x) greater than the maximal dose and dosage to be used in human studies. We further recommend that such safety pharmacology studies be completed before the medical imaging agent is introduced into humans (see Section III.B.1).

- We recommend that the NOAEL in short-term, repeated-dose toxicity studies in suitable animal species be at least twenty-five times (25x) greater than the maximal dose and dosage to be used in human studies.[20] Such short-term, repeated-dose toxicity studies can be performed either before the medical imaging agent is introduced into humans, or concurrently with early human studies, but we recommend that they completed before phase 2 (see Section III.B.1).

To establish these margins of safety, we recommend that the NOAELs be assessed in properly designed and conducted studies be appropriately adjusted. *Appropriately adjusted* means that dosage comparisons between animals and humans should be suitably modified for factors such as body size (e.g., body surface area) and otherwise adjusted for possible pharmacokinetic and toxicokinetic differences between animals and humans (e.g., differences in absorption for products that are administered orally).[21]

We recommend that the medical imaging agents granted a Group 1 designation undergo other nonclinical toxicological studies as described in Section III.B.1, such as genotoxicity, reproductive toxicity, irritancy studies, and drug-drug interaction studies. See section III.B.1 for details and timing sequence.

i. Additional considerations

FDA may still consider a medical imaging agent Group 1 even if its NOAELs are slightly less than the multiples specified above. For example, FDA will also take into consideration, among other things, how close the NOAELs are to the multiples specified above, the amount of safety information known about chemically similar and pharmacologically related medical imaging agents, the nature of observed animal toxicities, and whether adverse events have occurred

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[20] Short-term, repeated-dose toxicity studies may identify toxicities associated with accumulation of a medical imaging agent or its metabolites. In addition, even if such accumulation is not anticipated (e.g., non-metabolized medical imaging agents with short half-lives), short-term repeated-dose toxicity studies may identify toxicities caused by repeated toxic insults, each of which may be below the threshold of detection in expanded-acute, single-dose toxicity studies.

[21] For example, if drug elimination is based on a physiologic function that reflects blood flow, we then recommend that scaling on body surface area be used.

during initial human experience, including the nature of such adverse events (see Section IV.B.1.b).

ii. Formulations used in nonclinical studies

We recommend that the formulation used to establish safety margins in nonclinical studies be identical to the formulation that will be used in clinical trials and that is intended for marketing. We also recommend that any differences in the formulations used in the clinical trials and nonclinical studies be specified so that any impact on the adequacy of the nonclinical studies can be determined. Bridging studies may be helpful when changes in the formulation are apt to change the pharmacokinetics, the pharmacodynamics, or safety characteristics of the drug.[22]

In some cases, it may be infeasible or impractical to administer the intended clinical formulation to animals in multiples of the maximal human dose specified above (e.g., the volume of such an animal dose may be excessive). Sponsors are encouraged to discuss their plans with FDA before studies are initiated. In these cases, alternative strategies can be employed, such as dividing the daily dose (e.g., into a morning and evening dose), or by using a more concentrated formulation of the medical imaging agent, or the maximal feasible daily dose can be administered.

b. Results of initial human experience

In addition to those considerations described above for nonclinical studies, FDA also intends to consider the following when evaluating whether a medical imaging agent falls in Group 1.

- Safety issues were not identified during initial human use of the medical imaging agent in appropriately designed studies that include adequate and documented standard clinical safety evaluations. Identification of any adverse event during initial human use could be considered significant, particularly if those adverse events were not predicted from effects observed in animals. If adverse events occur at any time during human studies, we recommend that the medical imaging agent be reconsidered as a Group 2 medical imaging agent.

- We recommend that human pharmacokinetic studies be performed during phase 1 to allow adequate comparisons of exposure to be made between humans and the species used in the nonclinical studies. Such pharmacokinetic data can allow a more meaningful assessment of the relevance of the animal safety data (e.g., toxicokinetics).

[22] See guidance *S7A Safety pharmacology studies for human pharmaceuticals.*

### *2. Clinical Use Criteria*

Another way to be considered under Group 1 is by adequately documenting extensive prior clinical use without development of a safety signal. This means that there were no human toxicity or adverse events with clinical doses (including both mass and radiation doses, if applicable) of the agent, under conditions of adequate safety monitoring and the lack of human toxicity was adequately documented. We recommend that the methods used to monitor for adverse events be documented.

Group 1 designations based on the clinical-use criteria can occur at any time during drug development (e.g., after the conditions specified in this section have all been met).

## C. Procedures for Determining Whether a Medical Imaging Agent Falls Into Group 1 or 2

To be considered under Group 1 for a drug, sponsors are encouraged to write to the appropriate review division in CBER or CDER during nonclinical product development, or during phase 1 or 2, requesting designation.

## D. Radiation Safety Assessment for All Diagnostic Radiopharmaceuticals

### *1. General Considerations*

We recommend that an IND sponsor submit sufficient data from animal or human studies to allow a reasonable calculation of radiation absorbed dose to the whole body and to critical organs upon administration to a human subject (21 CFR 312.23(a)(10)(ii)). At a minimum, we recommend that the following organs and tissues be included in dosimetry estimates: (1) all target organs/tissues; (2) bone; (3) bone marrow; (4) liver; (5) spleen; (6) adrenal glands; (7) kidney; (8) lung; (9) heart; (10) urinary bladder; (11) gall bladder; (12) thyroid; (13) brain; (14) gonads; (15) gastrointestinal tract; and (16) adjacent organs of interest. When a diagnostic radiopharmaceutical is being developed for pediatric use, it may be appropriate to evaluate the radiation absorbed dose in all organs, rather than in selected organs. Moreover, we recommend that organ dosimetry be estimated for the pediatric age groups (e.g., neonates, infants, children, adolescents) in which the diagnostic radiopharmaceutical is intended to be used.

We recommend that the amount of radiation delivered by internal administration of diagnostic radiopharmaceuticals be calculated by internal radiation dosimetry. The absorbed fraction method of radiation dosimetry has been described by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and the International Commission on Radiological Protection (ICRP).

We also recommend that the methodology used to assess radiation safety be specified including reference to the body models that were used. We recommend that the mathematical equations used to derive the radiation doses and the absorbed dose estimates be provided along with a full description of assumptions that were made. We further recommend that sample calculations and all pertinent assumptions be listed and submitted. We recommend that the reference to the body, organ, or tissue model used in the dosimetry calculations be specified, particularly for new models being tested.

We recommend that safety hazards for patients and health care workers during and after administration of the radiolabeled product be identified, evaluated, and managed appropriately.

### *2. Calculation of Radiation Dose to the Target Organs or Tissues*

For established radionuclides used as diagnostic agents (e.g., TC-99m, IN-111), we recommend that the following items be determined based on the average patient:

- The amount of radioactivity that accumulates in the target tissue(s) or organ(s)
- The amount of radioactivity that accumulates in tissues adjacent to the target tissue(s) or organ(s)
- The residence time of the diagnostic radiopharmaceutical in the target tissue(s) or organ(s) and in adjacent regions
- For new radionuclide diagnostic agents, consult the appropriate review division.

### *3. Maximum Absorbed Radiation Dose*

We recommend that the amount of radioactive material administered to human subjects be the smallest radiation dose practical to perform the procedure without jeopardizing the benefits obtained.

We recommend that calculations anticipate possible changes in dosimetry that might occur in the presence of diseases in organs that are critical in metabolism or excretion of the diagnostic radiopharmaceutical. For example, renal dysfunction may cause a larger fraction of the administered dose to be cleared by the hepatobiliary system (or vice versa).

We recommend that possible changes in dosimetry resulting from patient-to-patient variations in antigen or receptor mass be considered in dosimetry calculations. For example, a large tumor mass may result in a larger-than-expected radiation dose to a target organ from a diagnostic radiopharmaceutical that has specificity for a tumor antigen.

We recommend that the mathematical equations used to derive the estimates of the radiation dose and the absorbed dose be provided along with a full description of assumptions that were made. We recommend that sample calculations and all pertinent assumptions be listed.

We recommend that calculations of dose estimates be performed assuming freshly labeled material (to account for the maximum amount of radioactivity) as well as the maximum shelf life of the diagnostic radiopharmaceutical (to allow for the upper limit of radioactive decay contaminants). We recommend that these calculations:

- Radiation doses from x-ray procedures that are part of the study (i.e., would not have occurred but for the study) should also be included. The possibility of follow-up studies should be considered for inclusion in the dose calculation.
- Be expressed as gray (Gy) per megabecquerel (MBq) or per millicurie (mCi) of radionuclide
- Be presented in a tabular format and include doses of individual absorbed radiation for the target tissues or organs and the organs listed above in Section IV.D.1.